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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,990	ISHIKAWA ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 19-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/1/01 & 3/4/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I claims 1-17 and 19-27, drawn to mutant of nucleoside-5'-phosphate producing enzyme, crystal, method of making mutants using atomic coordinates (first use), and nucleic acid encoding mutants, Class 435, subclass 193.

Group II claim 18, drawn to a method for producing inhibitor utilizing atomic coordinates (second use).

The inventions listed as Groups I, and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features. The special technical features for the invention of Group I and II are the atomic coordinates. Invention of Group I comprises claims directed to crystal, method of using the atomic coordinate to identify mutants of trans phosphorylation activity (first use), mutants, and nucleic acid encoding said mutants. Group is directed to a second method utilizing the atomic coordinates. Lack of unity of invention is lacking when there are multiple use of a special technical feature. 37 CFR 1.475, section (d) states:

> "If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and §1.476(c)."

During a telephone conversation with Ben Schnider on June 1, 2004 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-17, and 19-27. Affirmation of this election must be made by applicant in replying to this Office action. Claim 18 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. Applicant is required to furnish a drawing under 37 CFR 1.81. No new matter may be introduced in the required drawing.

New corrected drawings are required in this application because Figure 3 is of poor quality and the examiner could not see the binding site of the nucleoside phosphate being illustrated. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see for example page 28, lines 13, and 15). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Figure 1 is objected to because the amino acid residues defining the binding site are not identified by residue numbers from an amino acid sequence in the Figure or the Figure description.

Figures 2 and 9 are objected to because they are not in compliance with the sequence rules, which require the identification of any disclosed amino/nucleic acid sequence with a sequence identification number. Both Figures contain amino/nucleic acid sequences, which are not identified by a sequence identification number in the Figures or the Figure descriptions.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. The disclosed amino acid sequences in Figures 2 and 9 are not identified by sequence identification number in the Figures or the Figure descriptions, and they are not part of the paper copy of the sequence listing. In addition, the specification failed to identify a disclosed amino acid sequences by a specific sequence identification number at each occurrence, see for example page 2, last paragraph. The specification contains references to amino acid residues from a disclosed amino acid sequences without identifying the amino acid sequence with a sequence identification number. Applicants must perfect their compliance with sequence rules by filing a new paper copy of the sequence listing containing the amino acid sequences shown in Figures 2 and 9, new sequence listing in a Computer Readable Form (CRF), accompanied by a statement indicating the paper copy and CRF of the sequence listing are identical and contain no new matter. In addition, applicants are required to amend the specification to introduce the sequence identification numbers at each occurrence where the proteins are mentioned in the specification or

the claims such as in the Figure description of Figures 2 and 9, the examples 1-3, and claims 3, 5-16, and 20-22.

The disclosure is objected to because the word "Explanation" on page 37, line 19, should be -----Description----.

Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors, in particular, those resulting from poor translation and improper idiomatic English. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim does not further limit the claim from which it depends.

Claims 1-16 are objected to because they contain references to disclosed amino acid sequences such as the acid phosphatase from *Escherichia blatta* or *Entrobacter aerogenes,* or amino acid residues thereof without identifying the protein with a sequence identification number or the sequence identification number from which an amino acid residue is referenced. Applicants must bring the claims to compliance with sequence rules.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 19-22 are directed to all possible crystals of any, presumably, protein having any transphosphorylation activity and/or phosphatase activity (claim 19), any crystal of *Echirichia blattae* acid phosphatase and mutants thereof having the space group $P6_322$ (claim 20), $P2_12_12_1$ (claim 21), or $P3_121$ (claim 22). The specification, however, only provides three representative species of these crystals encompassed by

these claims. The wild-type acid phosphatase of SEQ ID NO: 1 crystallizes in the hexagonal space group $P6_322$, whereas its complex with molybdate and its double mutant G74D/I153T crystallizes in the trigonal space group $P3_121$ and the orthorhombic space group $P2_12_12_1$, respectively. It should be noted that three crystals were obtained under different crystallization condition and have different space group. There is no disclosure of how to change the crystallization conditions with changing the amino acid sequence of the acid phosphatase. The specification also fails to describe additional representative species of these additional crystals by any identifying structural characteristics or properties other than those recited in claims 20-22, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. Amending the claims 20-22 to include the sequence identification number of the protein of the crystal, i.e., SEQ ID NO: 1 would obviate this rejection.

Claims 1-4, 17, and 19-27 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to mutants of acid phosphatase having substantial sequence homology to the amino acid sequence of SEQ ID NO: 1 at positions corresponding to residues 16, 67-68, 78, 79, 96, 99, 100, 102-104, 106-108, 149-154, 157, 179, and 183 of SEQ ID NO: 1, nucleic acid encoding the same, vector, and host cell comprising said nucleic acid, and method for producing nucleoside-5'-phosphate using polyphosphoric acid, pyrophosphate, phenylphosphoric acid, carbamoyl phosphate, and acetylphosphoric acid. In addition, crystals of acid phosphatase derived from *Echirichia blattae* crystal containing SEQ ID NO: 2 in space group $P6_322$ (claim 20), the double mutant of SEQ ID NO: 1 (G74D/I53T) in space group $P2_12_12_1$ (claim 21), or Complex of SEQ ID NO: 1 and molibdate in space group $P3_121$. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all possible mutants of enzymes having transphosphorylation activity, which include any protein kinase, any nucleotide or nucleoside kinase, any alkaline or acid phosphatase having any substrate specificity from any biological source as well as any crystal of any protein or nucleic acid having any transphosphorylation activity. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of claims 1-4, 17 and 23-27 encompasses any mutant or chemically modified of any transphosphorylation activity including protein kinase/phosphatase, nucleotide and nucleoside kinases/phosphatases, and saccharine

kinases/phosphatases which can be used to catalyze the formation nucleoside-5'-phosphate having any chemical structure. Also, the claimed invention encompasses nucleic acid encoding said mutant enzyme, and vector and a host cell comprising said nucleic acid as well as a method to make any nucleotide-5'-phosphate. The specification provides guidance and examples in the form of an assay to crystallize the acid phosphatase from *E. blattae* of SEQ ID NO: 1 and its double mutants G74D/I153T, determine the three dimensional structure, identify the amino acid involved in binding nucleosides or nucleotide, identify a candidate residues for mutation to enhance the binding of a nucleotide or nucleoside, mutate SEQ ID NO: 1 and obtain several mutants which catalyze the formation of 5'-inosine phosphate, see examples. While molecular biological techniques and genetic manipulation to make any mutants of any transphosphorylation/phosphatase activity with known gene are known in the prior art and the skill of the artisan are well developed, knowledge regarding the three dimensional structures of the vast majority of the kinases and phosphatases, the ability of the vast majority of kinases and phosphatases to catalyze the formation of any 5'-nucleoside phosphate using any nucleoside and a chemically reactive phosphate donor such as pyrophosphate, and the kinases and phosphatases having one Lys, two Arg, and two His residues with distances between their Cα shown in Figure 1 is lacking. Thus, searching for a kinase or phosphatase capable of catalyzing the formation of any nucleoside-5'-phosphate from a nucleoside and chemically reactive phosphate donors other than ATP and identify mutants which improve said catalytic activity is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a kinase or phosphatase capable of catalyzing the formation of nucleoside 5'-phosphate using phosphate donor other than ATP is enormous. It should be noted the claimed genus of enzymes encompasses many distinct families of enzymes, which share no common structure (amino acid sequence homology or three dimensional structure homology) or function. Since routine experimentation in the art does not include screening vast numbers of kinases or phosphatases from a large number of biological and man-made sources where the expectation of obtaining the desired enzyme and its mutants is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding an enzyme having the desired catalytic activity, its three dimension structure. Without such guidance, the experimentation left to those skilled in the art is undue.

The nature and breadth of claims 19-22 encompasses any crystal of any enzymes including kinases, phosphatases and ribozymes with transphosphorylation activity. The specification provides guidance and examples in the form of an assay to obtain, presumably, the mature form of wild-type acid phosphatase from *E. blattae* corresponding to residues 19-249 of SEQ ID NO: 1 which crystallizes in the hexagonal space group $P6_322$, its complex with molybdate and its double mutant G74D/I153T which crystallize in the trigonal space group $P3_121$ and the orthorhombic space group $P2_12_12_1$, see examples 1-3. It should be noted that three crystals were obtained under different crystallization conditions and have different space group. While molecular

biological techniques and genetic manipulation to make any mutants of any enzyme with a known gene are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization conditions for any protein or nucleic acid is lacking. Thus, searching for a crystallization conditions to obtain an adequate crystal suitable for determining the three-dimensional structure of any protein is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a crystallization conditions is enormous. Obtaining a protein crystal suitable for structure determination by X-ray crystallography is not a routine experimentation becuase it require screening large number of crystallization conditions, which may include a trip to space. Since routine experimentation in the art does not include screening vast numbers of crystallization condition where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact amino acid sequence to be crystallized and the crystallization conditions which lead to a crystal suitable for structure determination by X-ray. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-17 and 19-27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The claims are generally narrative, indefinite and confusing, failing to conform to current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors, see for example the phrase "space around them allowing a binding of a nucleoside" in claim 1, "improved by predicting a binding mode to a nucleoside such as ...." and "and/or prosthetic factor etc" in claim 3, "put close to ....." in claim 8, the parenthetic statement of claims 5-8, and "hexagonal system" in claim 20, "rhombic system" in claim 21, and "trigonal system" in claim 22. The method of claim 17 does not contain any steps and one of ordinary skill in the art can't determine the metes and bounds of the claim. These are just a few examples of the non-idiomatic English in the claims. Applicants are required to rewrite their claims in idiomatic English.

(b) The phrases "nucleoside-5'-phosphate producing enzyme" in claims 1-3, 5-14, and 17; "improved nucleoside-5'-phosphate producing ability" in claims 1, 5-7, 9-11, and 17; "modifying a nucleoside-5'-phosphate producing enzyme" in claim 1; "transphosphorylation activity" in claims 1, 6, 7, 10, 11, 13, 14, and 17; and "shown in Figure 1 and a space around them allowing a binding of a nucleoside" in claims 1 and 2 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The following are the reasons for indefiniteness:

(i) The phrases "nucleoside-5'-phosphate producing enzyme" and "improved nucleoside-5'-phosphate producing ability" are repugnant to one of ordinary skill in the art because enzymes do not produce nucleotide-5'-phosphate. A reaction between a nucleoside and a phosphate donor produces the nucleoside 5'-phosphate. The enzyme is just a catalyst of the reaction, i. e., increases the rate of the reaction.

(ii) The term "improve" is a relative term and not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Inserting the phrase "relative to the wild-type enzyme" would obviate this rejection.

(iii) The phrase "modifying a nucleoside-5'-phosphate producing enzyme" is indefinite because there are many modification that can be made to an enzyme such as chemical modification, insertion, substitution, deletion, and combination thereof of one or more amino acid residue. For examination purposes only, the claim is taken to mean any enzyme having the stated activity(ies).

(iv) The phrase "transphosphorylation activity" is assumed to mean any protein or nucleic acid sequence, which is capable to catalyze a reaction involving the transfer of a phosphate group between a phosphate donor and acceptor such as phosphatases, and kinases.

(v) The phrase "shown in Figure 1 and a space around them allowing a binding of a nucleoside" is indefinite because it could mean "a binding site defined by the amino acid residues" or "a binding site nearby".

(c) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b)

a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1, 6-8, 11, 13, 14, and 17 recites the broad recitation transphosphorylation activity, and the claim also recites phosphatase activity, which is the narrower statement of the range/limitation. Phosphatase enzyme catalyzes the transfer of a phosphate group from a phosphorylated compound to water. Also, since the phosphatase is a catalyst, it is intrinsically has the reverse activity, i.e., the transfer of a phosphate group in solution to an acceptor molecule. Thus, a phosphatase has a transphosphorylation activity wherein the phosphate acceptor is water or other molecule.

(d) The phrase "such as" in claim 3 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

(e) The phrases "acid phosphatase derived from" in claims 3, 5-7, and 9-14; and "enzyme derived from" in claim 15 and 16 render the claims indefinite because the resulting claim do not clearly set forth the metes and bounds of the patent protection desired. The word "derived" is confuses the source of the enzyme. Any native or non-native phosphatase expressed in any host cell is derived from that host cell. Deleting the word derived would obviate this rejection.

(f) Claims 5-16 are confusing because the sequences from which the numbered amino acid residues are taken are not identified by a sequence identification numbers. That renders the claim indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The examiner is not clear whether this residues number from SEQ ID NO: 2, which is 249 amino acid residues including the pro-sequence of 18 amino acid residues, an amino acid sequence missing the pro sequence, or completely different amino acid sequence such as those in Figure 2. For examination purposes only, the number taken from a sequence of the mature acid phosphatase from *E. blattae* taught in U. S. Patent 6,015,697 (Mihara *et al.*) as SEQ ID NO: 8. For claims 15 and 16, the residues are assumed to correspond to the residues in the mature acid phosphatase from *E. blattae* of said SEQ ID NO: 8.

(g) Claim 17 is confusing and hard to ascertain its metes and bound. While the specification appears to describe the substrate's binding site defined by the amino acid described in Figure 1, i. e., the nucleoside's binding site, the specification has not identified the complete active site of the enzyme where the phosphate donor bind or the catalytic amino acid residues

involved in catalysis. It is not clear from which atom(s) to what atom(s) a distance of 10 Å would be measured. Neither the specification identify those amino acid residues within 10 Å of the active site or one of ordinary skill in the art can identify them from the three dimensional structure defined by the disclosed atomic coordinates. Thus, the claim is indefinite.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-14, 17, and 23-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Mihara *et al.* (see IDS: EP0857788A2).

Claims 1-14, 17, and 23-27 are rejected under 35 U.S.C. 102(e) as being anticipated by any of U. S. Patents 6,015,697; 6,207,435; and 6,355,472 (Mihara *et al.*, see IDS).

The cited U. S. Patent above and EP0857788 appear to be identical documents claiming the same foreign priority to Japanese patent applications 311103/96, filed November 21, 1996; and 161674/97, filed June 18, 1997. Thus, the rejections will be discussed relaying on citations from EP0857788A2 document.

Mihara *et al.* teach the nucleic acid sequence of SEQ ID NO's: 2 and 6 encoding the acid phosphatase from *Morganella morganii* and *Escherichia blattae* of SEQ ID NO: 3 and 7, respectively. Also, they teach the mature form of the acid phosphatase from *M. morganii, E. blattae,* and *Entrobacter aerogenes* of SEQ ID NO: 4, 8, and 24, respectively, see examples 8, 12, and 24. Example 14 describe a method of preparing 5'-inosinic acid using sodium pyrophosphate and inosine, and an *E. coli* expressing the *E. blattae* acid phosphatase at pH 4. Example 19 teaches several mutants *E. blattae* which have a higher efficincy in catalyzing the 5'-nucleotide formation. Table 12 describe several mutants made which include mutation of Ser-85 and Glu-135 of SEQ ID NO: 8 of Mihara *et al.* SEQ ID NO: 8 of Mihara *et al.* is identical to SEQ ID NO: 2 except for 18 amino acid residue missing at the N-terminus. Assuming the numbers in claims are referenced to the mature enzyme, i. e., the numbers according to SEQ ID NO: 8 of the Mihara reference, the Mihara reference teaches mutants of the mature acid phosphatase from *E. blattae* mutations to residues 69, 71, 72, 74, and 153 among others and their use in making nucleoside 5'-phosphate, and therefore, anticipates claims 1-7, 9-14, and 23-27. The additional limitation of comparing two structures, presumably, to identify residues corresponding to mutated residues in *E. blattae* does not have a patentable weight because the claim is directed to a product having specific

structure and it does not matter how the product is made or the structure is identified (claim 8). Similarly, claim 17 is included in this rejection because Mihara *et al.* taught mutation of amino acid residues 69, 71, 72, 74, and 153 of the mature acid phosphatase from *E. blattae* which are presumed to be within 10 Angstrom units from the active site.

Claims 1-14, 17, and 23-27 are rejected under 35 U.S.C. 102(b), and (e) as being anticipated by Mihara *et al.* (see IDS: EP0832970), and U. S. patent 6,010,851 ('851, Mihara *et al.*, see IDS), respectively.

U. S. Patent 6,010,851 has matured from serial number 08/750,145, which is a national stage application of PCT/JP96/01402. It is an identical document to EP0832970, which also corresponds to PCT/JP96/01402. Since the two document are identical, the rejections will be discussed relaying on citations from EP0832970 document.

The EP document teaches several nucleic acid sequences encoding the acid phosphatases of SEQ ID NO: 20 (*E. aerogenes*), 22 (*Klebsiella planticola*), and 24 (*Serratia ficaria*) and the corresponding amino acid residues, see example 24. Also, it teaches method of making nucleoside 5'phosphate using said acid phosphatases, see claim 25. For example, SEQ ID NO's: 20 and 22 are highly homologous to the acid phosphatase from *E. blattae* (~ 90% sequence homology to SEQ ID NO: 2 of the instant application), and thus, are considered mutants of SEQ ID NO: 2. Residue 90 of SEQ ID NO: 20 and 22 is alanine residue, which correspond to residue 72 of the mature enzyme from *E. blattae*. In addition, example 19 of the EP document teaches mutants of the mature acid phosphatse from *E. blattae* at position 74 and 153, both are believed to be in the binding site or with 10-angstrom units thereof. Thus, the nucleic and amino acid sequences taught in the EP document anticipate claims 1-14, and 23-27.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mihara *et al.* or any of the corresponding U. S. Patents 6,015,697; 6,207,435; and 6,355,472 (all Mihara *et al.*, see IDS).

The teaching of Mihara *et al.* and the corresponding U. S. patents are summarized above.

Mihara *et al.* and the corresponding U. S. patents provide one of ordinary skill in the art with motivation to mutate the acid phosphatase to produce an enzyme capable of catalyzing the formation of a nucleoside 5'-phosphate. Also, they teach the nucleic acid and amino acid sequences of several bacterial acid phosphatase including those from *E. blattae* and *E. aerogenes.* The amino acid sequences of the two acid phosphatases are >90% homologous and most of the differences are at the N-termini. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention, to align the two sequences by well-known methods in the art, identify the amino acids in the phosphatase from *E. aerogenes* which correspond to the amino acid residues mutated and taught by Mihara *et al.* to produced the desired results, mutate the amino acid residues in the phosphatase from *E. aerogenes* to use in a method to make nucleoside 5'-phosphate as taught by Mihara *et al.* Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,207,435 ('435). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of '435 is directed to any mutant acid phosphatase of SEQ ID NO: 4, 8, 24, 26 and 28, which has lower K_m value for a nucleoside measured for a reaction between said nucleoside and a phosphate donor catalyzed by the mutant enzyme relative to that of the wild type. SEQ ID NO: 8 and 24 are the amino acid sequences for the mature acid phosphatase from *E. blattae* and the proenzyme from *Entrobacter aerogens*, respectively. Claim 2 of the '435 is directed to specific mutation site, residues 69, 71, 72, 74, and 153 of SEQ ID NO: 8, which are believed to satisfy the structure requirements of claim 1.

Claims 23-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,355,472 ('472). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of '472 is directed to nucleic acid encoding any mutant acid phosphatase of SEQ ID NO: 4, 8, 24, 26 and 28, which has lower K_m value for a nucleoside measured for a reaction between said nucleoside and a phosphate donor catalyzed by the mutant enzyme relative to that of the wild type. SEQ ID NO: 8 and 24 are the amino acid sequences for the mature acid phosphatase from *E. blattae* and *Entrobacter aerogens*, respectively. Claim 4 of the '472 is directed to specific mutation site, residues 69, 71, 72, 74, and 153 of SEQ ID NO: 8, which are believed to satisfy the structure requirements of claim 1 from which claims 23-25 are dependent.

Claims 26 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U. S. Patent No. 6,015,697 ('697). Although the conflicting claims are not identical, they are not patentably distinct from each other because independent claims 1, and 8 of '697 are directed to a method of making nucleoside 5'-phosphate using any mutant acid phosphatase of SEQ ID NO: 4, 8, 24, 26 and 28, which has lower K_m value for a nucleoside measured for a reaction between said nucleoside and a phosphate donor catalyzed by the mutant enzyme relative to that of the wild type to catalyze the reaction. SEQ ID NO: 8 and 24 are the amino acid sequences for the mature acid phosphatase from *E. blattae* and the proenzyme from *Entrobacter aerogens*, respectively. Dependent claims 2, 7, 12, and 13 of the '697 are directed to specific mutation site, residues 69, 71, 72, 74, 151, and 153 of SEQ ID NO: 8, which are believed to satisfy the structure requirements of claim 1 from which the method claims 26 and 27 are dependent.

Claims 1-14, and 23-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8, 9, 11, 13, 14, 16, 18, 19, 21, 23, 24, and 26 of U. S. Patent No. 6,010,851 ('851). Although the conflicting claims are not identical, they are not patentably distinct from each other. Independent claim 1 and its dependent claims 2-6 of the '851, of the '851 are directed to

a method of making nucleoside 5'-phosphate using SEQ ID NO: 4, 11, 18, 20, 22, and 24 and their mutants having lower K_m value for a nucleoside measured for a reaction between said nucleoside and a phosphate donor catalyzed by an acid phosphatase or its mutant enzyme relative to that of the wild type to catalyze the reaction. SEQ ID NO: 11 and 22 are the amino acid sequences for the mature acid phosphatase from *E. blattae* and the proenzyme from *Entrobacter aerogens*, respectively. The two sequences are highly homologous (>90%) in the mature region of the sequence. Thus, the Ala-90 of SEQ ID NO: 22 corresponds to Ser-72 of SEQ ID NO: 11 which is part of the binding site, and thus, SEQ ID NO: 22 is considered a mutant of SEQ ID NO: 11 (claims 26 and 27). Claim 6 of the patent limits the method to specific mutants, e.g., residues 74 and 153 of SEQ ID NO: 11 believed to be within the ranges shown in Figure 1 or in the space around them (claims 26 and 27). Claims 8, 9, 11, 13, 14, 16, 18, 19, 21, 23, 24, and 26 are claiming the phosphatase mutants of SEQ ID NO: 11 including SEQ ID NO: 22, nucleic acid encoding said phosphatase, recombinant DNA and microorganism (1-14 and 23-25), respectively.

Claims 20-22 would be allowable, if they are amended to identify the protein in the crystal by a sequence identification number, remove the parenthetic statement of claim 22, and substitute the word "system" by ----crystal---- and "rhombic" in claim with ----orthorhombic----.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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